Adult Presentation of PHACES Syndrome

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Summary

A significant percentage of children with hemangiomas may have PHACES syndrome which refers to the association of posterior fossa malformations, facial hemangiomas, arterial cerebrovascular abnormalities, cardiovascular anomalies, eye abnormalities and ventral defects like sternal clefting or supraumbilical raphe. A variety of factors have led to under diagnosis of PHACES syndrome in the past including lack of awareness and limited imaging modalities. Also, patients with PHACES syndrome with arterial cerebrovascular abnormalities can present with acute ischemic stroke. However, these patients usually present before one year of age. We describe a 29-year-old woman with no history of cerebrovascular disease who initially presented with symptoms of a stroke and was subsequently diagnosed to have PHACES syndrome exhibiting an array of multiple unusual imaging findings. We also discuss the current literature and recommendations about PHACES syndrome.

Introduction

PHACE refers to the association of posterior fossa malformations, facial hemangiomas, arterial cerebrovascular abnormalities, cardiovascular anomalies, and eye abnormalities [1]. PHACES is now used as ventral defects like sternal clefting or supraumbilical raphe are known to occur in some patients [2]. Abnormal neural crest migration has been suggested to cause PHACES syndrome during early embryonic development. It is rare that all abnormalities occur in one patient and partial phenotypic expression is the norm. Recently, standardized criteria were proposed for diagnosis of the PHACES syndrome [3]. The natural history and long-term prognosis of PHACES patients remains unknown. However, the cerebrovascular abnormalities are an important determinant of prognosis because of their propensity to cause acute ischemic events. Patients with PHACES who develop acute ischemic stroke usually present before one year of age [4].

We describe a 29-year-old woman with no history of cerebrovascular disease who initially presented with symptoms of a stroke and was subsequently diagnosed to have PHACES syndrome exhibiting an array of multiple unusual imaging findings. A review of current literature on PHACES syndrome is also presented.

Case Report

A 29-year-old woman presented with sudden onset of left upper and lower extremities weakness along with numbness of the left face, arm and leg. On physical examination, there was a prominent facial hemangioma over the left eye and eyebrow (Figure 1) along with mild left-sided hemiparesis and diminished sensation predominantly over the left face and extremities. Her past history was significant for amenorrhea for which she was evaluated in adolescence at an outside facility. During that work up she was diagnosed with a Dandy-Walker malformation and further investigation was not pursued.

The patient received a comprehensive multimodality imaging work up. There were multiple posterior fossa anomalies including partial

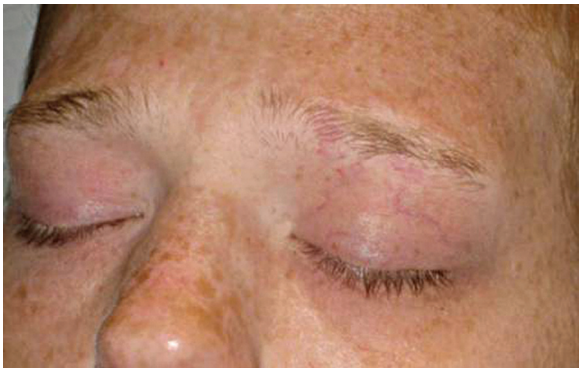


Figure 1 Photograph showing remnant of a facial hemangioma, most prominently seen over the left eye.

agenesis of the cerebellar vermis, hypoplasia of the left cerebellar hemisphere along with a large posterior fossa arachnoid cyst as well as arachnoid cysts along the bilateral temporal lobes (Figure 2A,B). An amorphous calcific density was seen projecting over the right suprasellar cistern which was later demonstrated to be calcifications in the region of moya-moya like collateral vessels (Figure 2C). Bilateral temporal bone developmental anomalies were also demonstrated (Figure 2D). Evaluation with diffusion weighted imaging demonstrated multiple punctate areas of restricted diffusion in deep temporal, parietal and occipital white matter compatible with acute ischemia (Figure 3A-D). Multiple complex cerebrovascular anomalies were seen: the right internal carotid artery (ICA) demonstrated an aberrant course through the temporal bone with its proximal vertical portion extending far laterally to abut the medial wall of the middle ear with a thin bony margin between the tympanic cavity and the vessel. There was complete absence of the contralateral left ICA with corresponding absence of the left bony carotid canal. Collateral circulation, at least partially arising from the left external carotid artery via the artery of the foramen rotundum, reconstituted the cavernous and supraclinoid portions of the left ICA (Figure 4A-F). The supraclinoid portion of the right ICA terminated in a curvilinear fusiform aneurysmal dilatation with thrombosis of the most distal portion. Extensive collateral circulation was seen in the vicinity of the fusiform dilatation forming a moyamoya appearance (Figure 5A-D). The proximal basilar artery (BA) bifurcated into two small caliber anterior inferior cerebellar arteries (AICA). No basilar artery was appreciated beyond that point. A fetal origin of the left posterior cerebral artery was visualized. There was extensive collateral circulation in the expected location of the right posterior cerebral artery, but no distinct vessel was identified (Figure 6A,B). Anomalous aortic arch anatomy was also seen; the left subclavian artery arose from the medial wall of the aortic arch, far more posterior than expected. The right subclavian artery also had an aberrant course, with its proximal portion taking a U-shaped bend posterior to the right thyroid lobe before extending in a normal fashion to the right upper extremity (Figure 4E,F).

The patient was ultimately referred for an external-to-internal carotid artery bypass. She had an uneventful recovery and recently completed her two-year follow-up. She has returned to normal functioning (Modified Rankin Scale of 0) and has not experienced additional neurological events.

Discussion

Hemangiomas are one of the most common childhood tumors and are found in up to 10% of children by one year of age. Most of the hemangiomas regress spontaneously. 7% of infants with hemangiomas have associated abnormalities and it is estimated that half of these infants (3.5% of total) may have PHACES syndrome. Recently, a multicenter prospective study demonstrated that up to one third of infants with large facial hemangiomas have extracutaneous abnormalities consistent with a diagnosis of PHACES syndrome [5].

The association of facial hemangiomas and intracranial abnormalities including vascular malformations was first described by Pascual Castroviejo in 1978 [6]. Frieden, in 1996, proposed the acronym PHACE, for an association

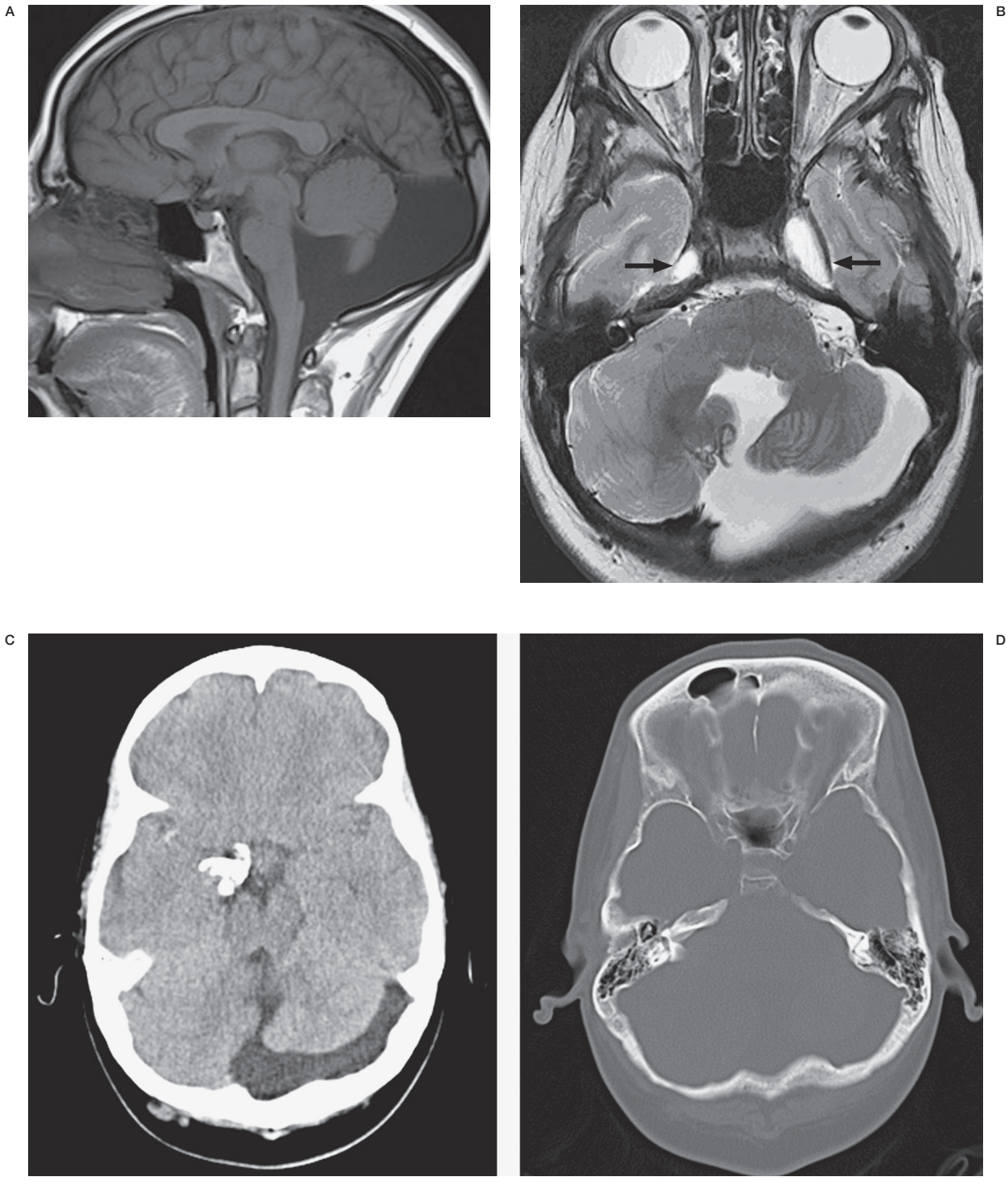


Figure 2 A) Sagittal T1-weighted image of the brain demonstrates a posterior fossa anomaly with vermian hypoplasia and expansile arachnoid cyst. B) Axial T2-weighted image demonstrates posterior fossa arachnoid cyst with cerebellar and vermian hypoplasia. Arachnoid cysts in bilateral Meckel's caves can be appreciated (arrows). Note asymmetry of internal auditory canals. C,D) Non-contrast head CT demonstrates an amorphous hyperdense partially calcific structure projecting upon the right suprasellar cistern. There is demonstration of left cerebellar hypoplasia. Bone window image demonstrates abnormality of bilateral temporal bones is again noted including hypoplasia of the right and aplasia of the left internal auditory canal (IAC). Hypoplasia of the left bony carotid canal is not shown.

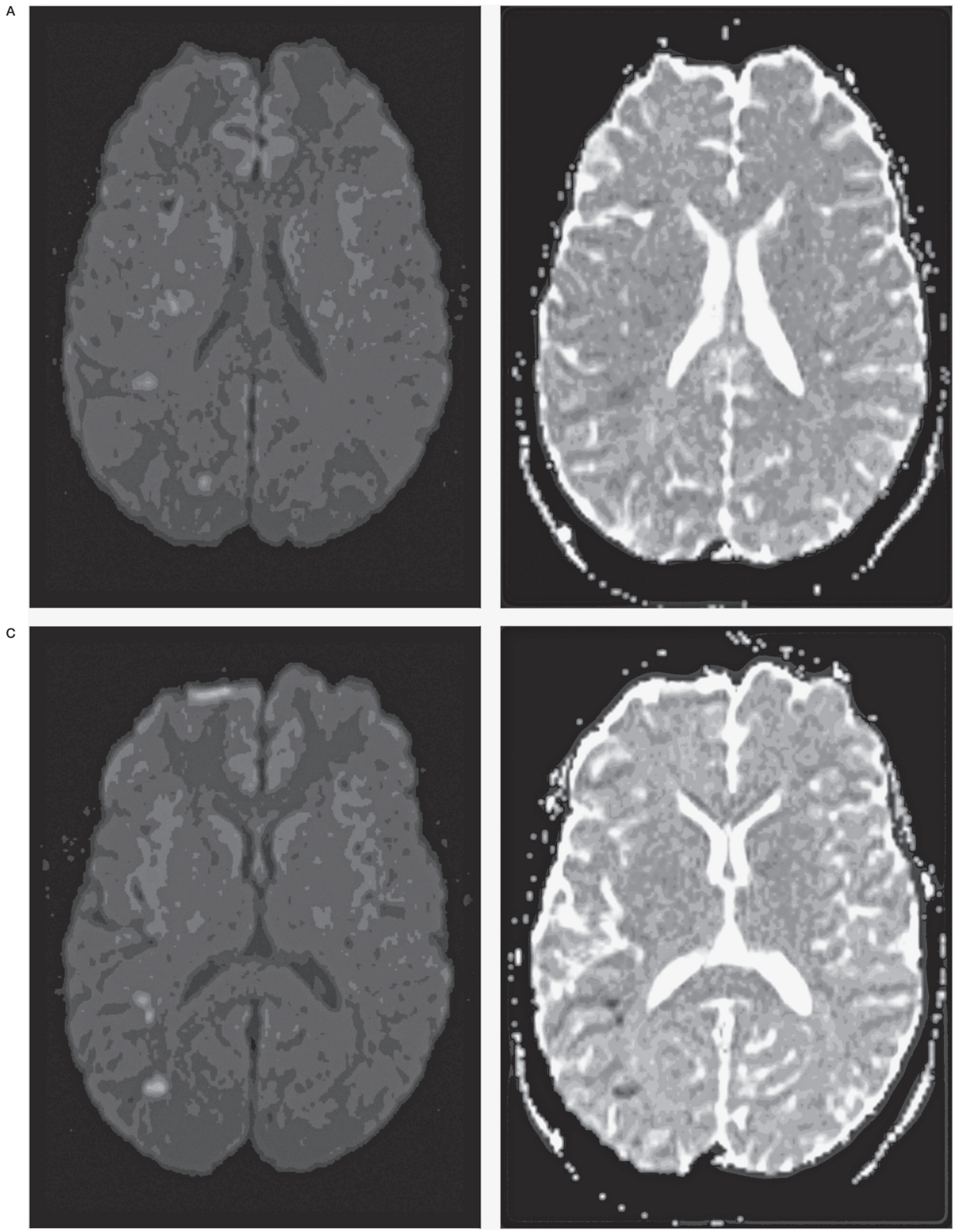


Figure 3 A-D) Diffusion-weighted imaging demonstrates multiple punctate areas of restricted diffusion in deep temporal, parietal and occipital white matter compatible with acute ischemia.

characterized by posterior fossa malformations, hemangiomas, arterial anomalies, coarction of aorta and cardiac defects, and eye abnormalities [1]. The term has since been lengthened to PHACES to include midline sternal and raphe defect which may be present in some cases.

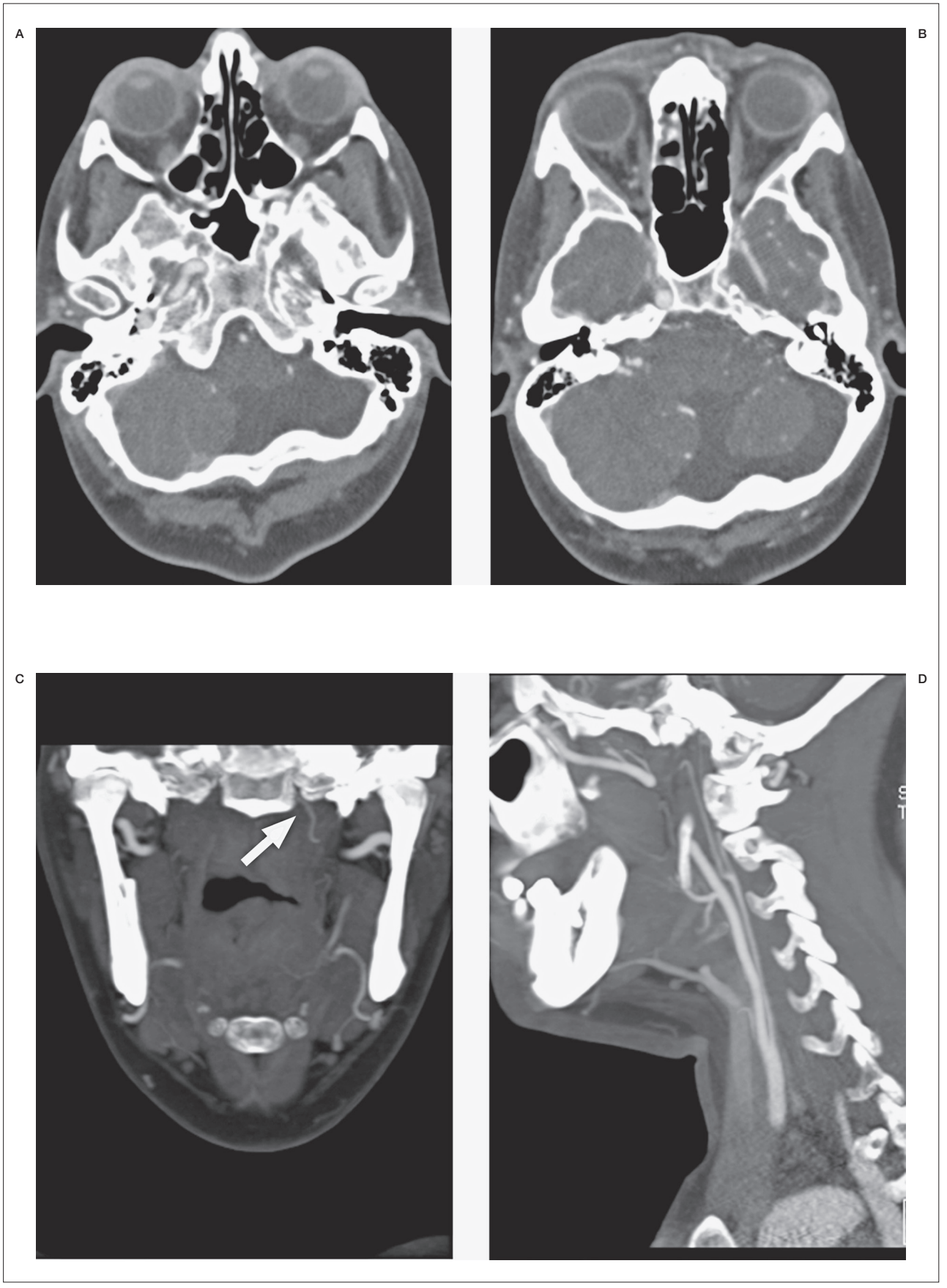
PHACES syndrome represents a spectrum of anomalies, but simultaneous presence of all anomalies is the exception. 70% of children with PHACES have only one extracutaneous manifestation of the syndrome. Although a relatively rare syndrome, PHACES has probably been under-recognized in the past. Some of the causes include lack of complete investigations (vascular imaging) in neurologically asymptomatic patients and misdiagnosis as Sturge-Weber syndrome [7]. Our patient was diagnosed with a Dandy-Walker malformation in her teenage years. As our patient did not have any neurologic symptoms previously, further imaging was not pursued. In the Dandy-Walker complex there is no overall gender difference, however, if there is an accompanying hemangioma, there is a strong female predominance, as in PHACES syndrome. It has been suggested that there may be a significant proportion of patients with a Dandy-Walker malformation that may have unrecognized PHACES syndrome [2].

PHACES syndrome shows a female to male predilection of 9:1. There is no definite evidence of a familial tendency although an X chromosome linked dominant single gene etiology has been suggested with lethality in males. Non-random maternal X chromosome inactivation has been hypothesized to account for asymptomatic carriers [8].

Given the many manifestations of PHACES syndrome, it was necessary to formulate guidelines for its diagnosis. Recently consensus criteria were agreed upon. PHACES syndrome requires presence of a facial hemangioma >5 cm^2 along with one major or two minor criteria. If the patient has greater than one anomaly within a given organ system, it will count as a single criterion only. A separate category of possible PHACES syndrome has been described. The major and minor criteria for our patients have been listed in Table 1 [3].

The etiology of PHACES syndrome is still unknown. However, the cutaneous and extracutaneous manifestations appear to be temporally and regionally linked by an insult occurring in early embryogenesis. The large hemangiomas exhibit a growth pattern corresponding to early embryonal facial segments [9]. The cerebrovascular anomalies also appear to be due to an embryonic insult due to persistence of embryonal arteries and arrest of normal vasculature development. The vascular abnormalities tend to occur ipsilateral to the cutaneous hemangiomas and in some cases bilaterally [10]. The most conspicuous vascular malformations are nearest to the facial hemangioma or are in direct relation to intracranial feeder vessels. Hemangiomas involving the upper half of the face are associated with abnormalities of the brain, cerebral vasculature or the orbits. Hemangiomas in a mandibular distribution are associated with ventral developmental defects. Isolated hemangiomas in a maxillary distribution are least likely to be associated with PHACES syndrome [10]. An insult to the neural crest and neural plate cells has been postulated as a possible mechanism. Neural crest cells (NCC) contribute to formation of all the systems affected by PHACES syndrome and abnormal NCC may result in the phenotypes associated with PHACES syndrome [11,12]. The putative insult must occur before the migration of NCC (and adjacent mesodermal cells) to account for the widespread lesions. A developmental error occurring before six weeks of gestation is thought to be likely. A developmental-field defect results from errors within morphoregulatory genes, like HOX and Eph, that determine a constellation of developmental anomalies in a spatially coordinated, temporally synchronous manner [7].

The cerebrovascular anomalies are the most common extracutaneous manifestation of PHACES syndrome. Predominant involvement of the arterial system distinguishes PHACES from other neurocutaneous syndromes. The arterial anomalies in PHACES syndrome consist of these following categories (in decreasing order of prevalence): 1. dysplasia, 2. narrowing, 3. aberrant course or origin and 4. persistence of embryonic anastomoses [3,10]. Burrows et al. first demonstrated presence of progressive occlusive disease in a subset of PHACES patients. Progressive vasculopathy may be related to the proliferative phase of hemangioma evolution [13]. The hemangiomas are not apparent at birth, grow rapidly according to embryonal facial segments with production of vascular growth factors (proliferative phase) and then undergo involution over many years. It has been postulated that vascular growth factors elaborated by the hemangioma itself may constitute the putative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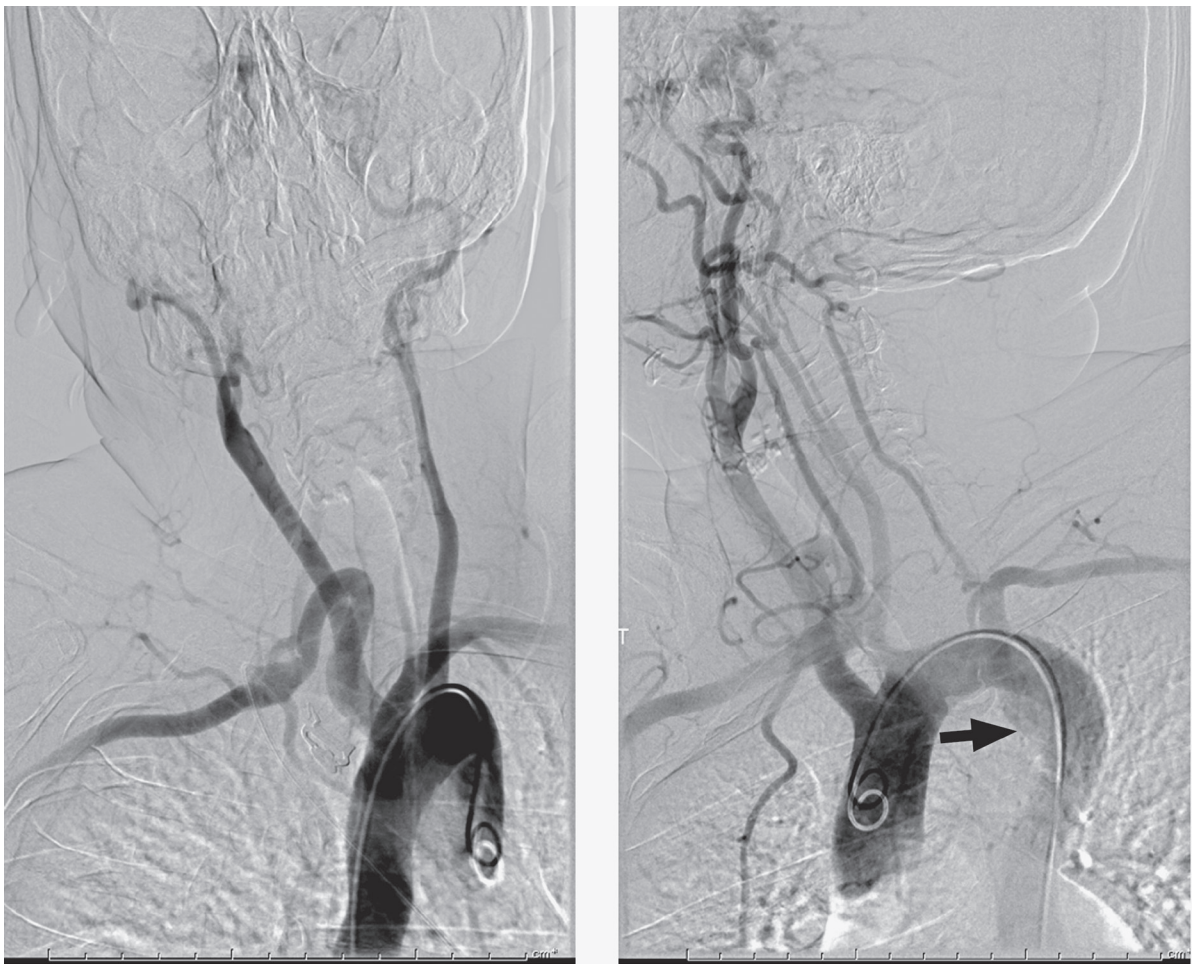

Figure 4 A-D) Axial, coronal and sagittal maximum intensity projections (MIPs) of CT angiography (CTA) of the neck demonstrate aplasia of the left internal carotid artery (ICA) and the abnormal lateral course of right ICA. The ascending pharyngeal artery extends cranially with an anastomosing branch (through foramen of rotundum) to the cavernous portion of left ICA (arrow). E-F) AP oblique and lateral digital subtraction angiography (DSA) images demonstrate aplasia of the left internal carotid artery (ICA) and left ascending pharyngeal artery extending cranially with an anastomosing branch to the cavernous portion of left ICA. There is also demonstration of aneurysmal widening of the right carotid terminus prior to continuation into a moya-moya like mesh of vessels. Abnormal origins and courses of the subclavian vessels are also partially demonstrated (arrow points towards abnormal origin of the left subclavian artery from the postero-medial aortic arch).

insult related to cerebral arteriopathy. Congenital vascular abnormality could result from a diffusible factor produced during the embryonic phase of hemangioma formation whereas the same modulator elaborated during the proliferative phase of hemangioma growth would lead to steno-occlusive vascular disease. However, the "growth factor" hypothesis fails to explain the origin of the hemangioma itself and development of symptomatic steno-occlusive disease long after hemangioma involution [14].

Another hypothesis has been proposed which involves improper signaling mechanisms. The hemangiomas seen in infants seldom start in utero, then grow exponentially and usually regress spontaneously without inflammatory manifestations. This unrepressed proliferation and delayed apoptosis also suggest improper signaling from vascular cells which should have not persisted and become proliferative. Proliferation without remodeling may lead to luminal reduction [2]. As our case presented at 29 years of age, long after the proliferative phase of hemangioma evolution (it was still not completely involuted), the presence of steno-occlusive disease and moya-moya collateral formation is more likely due to improper signaling mechanisms.

The neurologic signs and symptoms of PHACES syndrome typically present in infan-

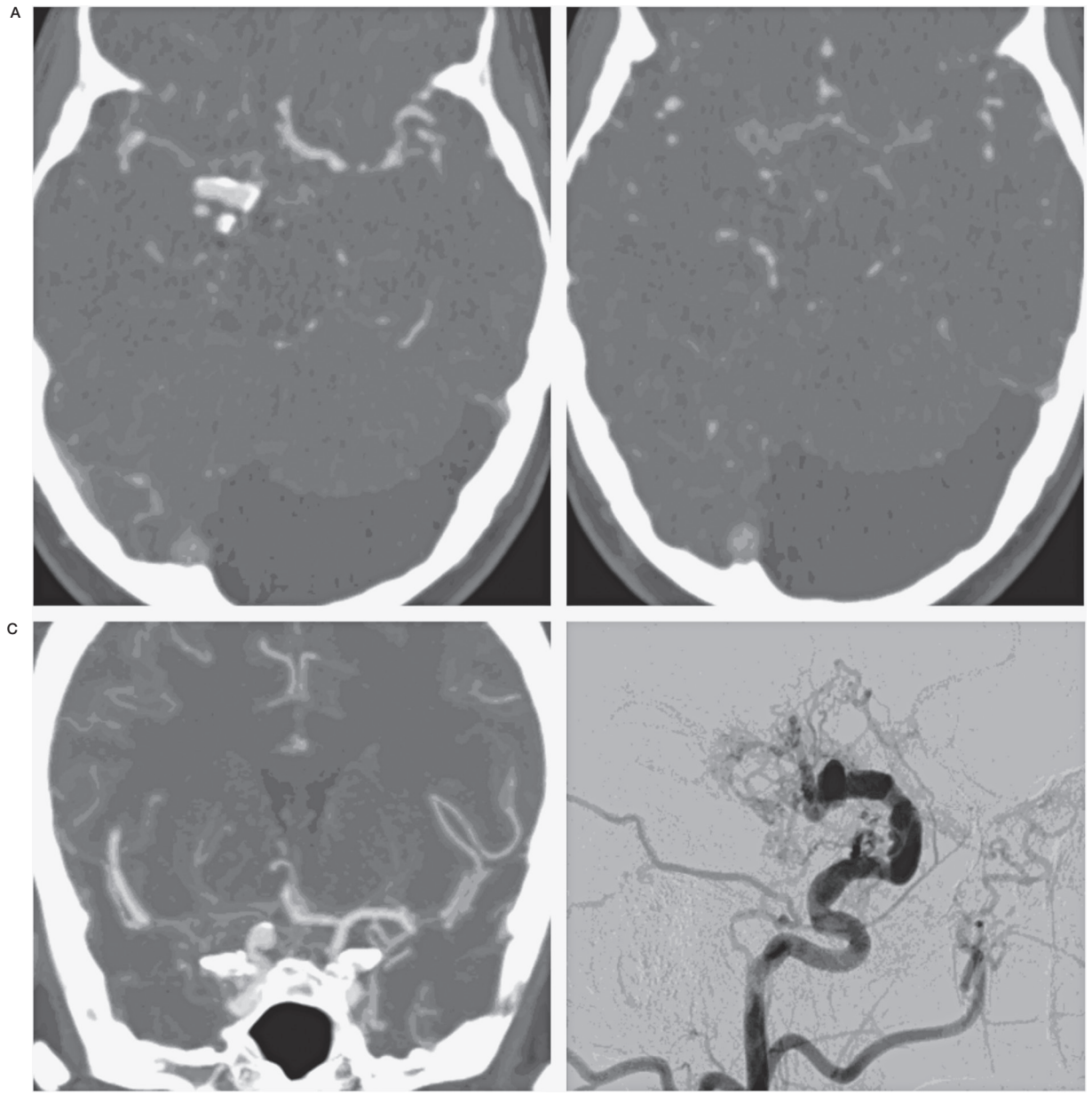

Figure 5 A-D) Axial and coronal CT angiography images along with lateral digital subtraction angiography images demonstrate aneurismal widening and thrombosis of the right carotid terminus prior to its continuation into a moya-moya like mesh of vessels.

cy or childhood and may be related to congenital lesions of the cerebrum/cerebellum and/or acute ischemic stroke (AIS). AIS is rare in children and difficult to diagnose. There are many factors that may contribute to the under-recognition of AIS in infants with PHACES association. The clinical diagnosis of stroke is often delayed in children. Headaches and aphasia are very difficult to appreciate in a child who has not yet developed language skills. Subtle neurologic changes, especially in patients with PHACES association and baseline neurologic impairment related to structural anomalies of the cerebellum, may not be appreciated. Cerebrovascular abnormalities may not be the only explanation for this increased risk of stroke in PHACES patients [15]. Our case presented at 29 years of age and the diagnosis was not considered earlier when she was found to have a Dandy-Walker malformation. While this reiterates the need for complete imaging evaluation in patients with large facial hemangiomas when

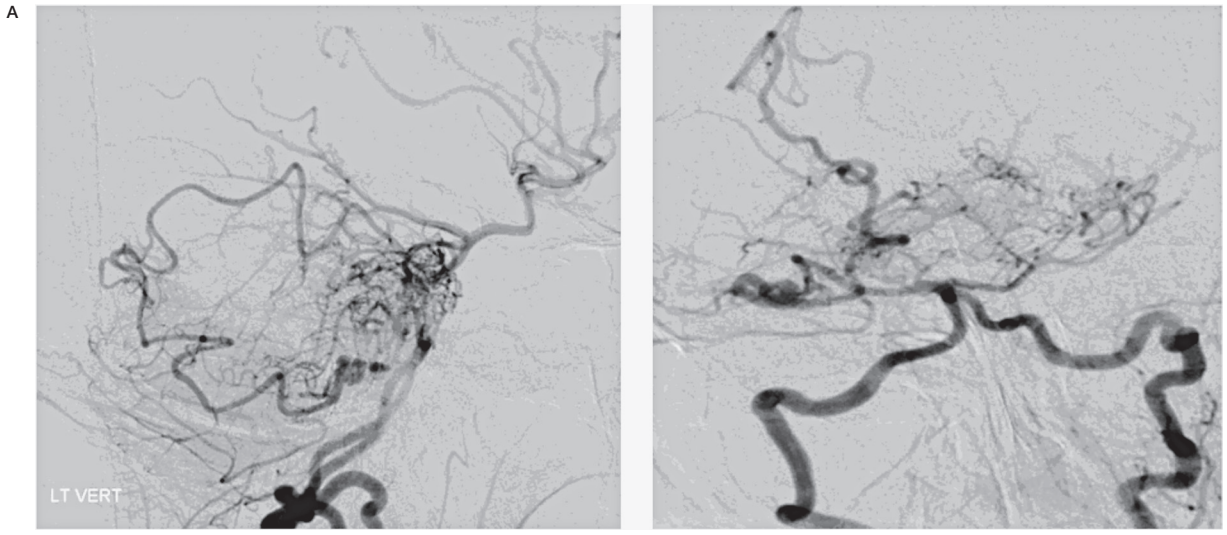

Figure 6 A,B) Lateral and PA view of the posterior circulation demonstrate bifurcation of proximal basilar artery into two small anterior inferior cerebral arteries with no definite basilar artery beyond the bifurcation. Fetal origin of the left posterior cerebral artery was demonstrated. Extensive collateral circulation was seen in the expected position of right posterior cerebral artery but no distinct vessel was identified.

Table 1 **A list of major and minor criteria for PHACES syndrome diagnosis present in our patient. The cerebrovascular abnormalities have been classified under the recently described broad categories** [3,10].

	Cerebrovascular	**Brain Structural Malformations**	**Cardiovascular**	**Ocular**	**Ventral or Midline**
Major	Dysplasia of large cerebral artery (Right ICA), Arterial stenosis or occlusion with or without moya moya collaterals (Right ICA and basilar artery), Absence or moderate to severe hypoplasia of the large cerebral arteries (Left ICA)	Left cerebellar hypoplasia along with dysplasia of right cerebellar peduncle and right pons, Dandy-Walker complex	None	None	None
Minor	None	None	Aberrant origin of left subclavian artery	None	None

they are young, it also alerts us to the possibility of considering the diagnosis of PHACES in a young, otherwise healthy adult who presents with symptoms of acute stroke. A history of presence of facial hemangiomas during childhood would be greatly beneficial in this case.

The therapies used to treat cutaneous hemangiomas including systemic corticosteroids and interferon 2 alpha may play a role in the onset of neurologic symptoms in patients with accompanying cerebrovascular abnormalities. Corticosteroids and interferon might help in regression of the hemangioma by inhibiting angiogenesis which could disrupt formation of much needed collaterals [16]. Revascularization techniques are important in cases like ours where there is a long life expectancy and there is need to restore adequate cerebrovascular flow. Our patient received an ECA-ICA bypass and has subsequently resumed a normal quality of life. We feel it is important to involve the full spectrum of specialties including neurology, pediatrics, neuroradiology, neurosurgery and dermatology in treatment of PHACES syndrome patients.

Conclusion

PHACES syndrome is a rare congenital neurocutaneous syndrome. It usually presents during infancy and childhood.

A precise estimate of its incidence is unknown as it may have been underdiagnosed in the past.

The oldest known case of a PHACES patient who had acute ischemic stroke was 14 years. We present a case of a previously healthy 29-year-old patient who presented with stroke and was found to have PHACES syndrome. We feel that this case adds to prevalent knowledge about PHACES syndrome and underlines the importance of obtaining a full diagnostic work up in patients with large facial hemangiomas.

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